## REMARKS

### I. Amendments

Claim 12 has been amended and claims 1-11, 13-15 and 17-19 are canceled herein. New claims 21-30 are being added. The amended claim and newly added claims do not add or constitute new matter and are supported by the application as originally filed. More particularly, support for the amendment to claim 12 may be found, for example, at page 20, line 11 through page 21, line 14 and page 53, lines 8-14 of the specification. Support for claims 21-25 may be found, for example, at page 4, lines 25-27, page 5, lines 6-13, page 8, lines 21-22, page 12, line 28 through page 16, line 31 and page 53, lines 8-14 of the specification. Support for claims 26 and 29-30 may be found, for example, at page 10, line 21 through page 12, line 6, and 53, lines 8-14 of the specification. Additionally, support for claims 27-28 may be found, for example, at page 12, line 29 through page 13, line 11, of the specification.

Amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later-filed divisional, continuation or continuation-in-part application.

Upon entry of the amendments, claims 12 and 21-30 are pending in the instant application.

### II. Objections

The Examiner objected to claim 2 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to limit the subject matter of a previous claim. The Examiner asserts that it is unclear how a screening marker differs from a selection marker, and therefore claim 2 fails to limit the subject matter of claim 1. Applicant respectfully disagrees. The definition and distinction between the terms "selectable marker" and "screening marker" are clearly set forth at, for example, page 11, lines 23-27 and page 14, lines 16-18 of the instant specification. However, the current claims do not recite "screening marker" and therefore render the Examiner's objection moot.

## III. Rejections

### *A. Rejection under 35 U.S.C. § 112, first paragraph*

The Examiner rejected claims 11-15 under 35 U.S.C. 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to make and/or use the invention. Applicant respectfully traverses this rejection. In view of the cancellation of claims 11 and 13-15, the Examiner's rejection of these claims under 35 U.S.C. 35 U.S.C. § 112, first paragraph are moot. Claim 12 has been amended to recite a method of identifying an agent that modulates a neuromuscular phenotype associated with NPY6, by using transgenic mice having a disruption in NPY6. In view of this amendment, the Examiner's rejection on the basis that the specification does not teach a specific method in determining the expression or function of NPY6 receptor in a NPY6 receptor knockout animal is rendered moot.

The Examiner rejected claims 5-10 and 17-19 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable one skilled in the art to make the invention commensurate with the scope of the claims. Applicant respectfully traverses this rejection. In view of the cancellation of these claims and the newly added claims, the Examiner's rejections of claims 5-10 and 17-19 under 35 U.S.C. § 112, first paragraph are moot.

The Examiner further rejected claim 17 under 35 U.S.C. § 112, first paragraph, asserting that the specification contains subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that the written description requirement was not satisfied for the claimed genus of "NPY6 receptor or homolog genes." Applicant respectfully disagrees. However, the current claims refer to murine NPY6 receptor gene and do not recite NPY6 "homologs." Therefore, Examiner's rejection is rendered moot.

Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 112, first paragraph. Applicant submits that amended claim 12 and new claims 21-30 fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

### *B. Rejection under 35 U.S.C. § 112, second paragraph*

The Examiner rejected claims 1-4, 9 and 10 under 35 U.S.C. § 112, second paragraph, for

allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicant respectfully traverses this rejection.

The Examiner asserts that the arrangement of the target construct is unclear. Applicant submits that the new claims clearly set forth the relative arrangement of the elements of the targeting construct, rendering the Examiner's rejection moot.

In rejecting claim 2, the Examiner asserts that it is unclear what the term "screening marker" encompasses, and how a "screening marker" differs from a "selection marker". Applicant respectfully disagrees. As discussed above, the definition and distinction between the terms "selection marker" and "screening marker" are clearly set forth at, for example, page 11, lines 23-27 and page 14, lines 16-28 of the instant specification. However, the current claims do not recite either "selection marker" or "screening marker." The current claims instead recite the term "selectable marker," which term is clearly defined in the specification at, for example, page 9, lines 8-13. Therefore, Examiner's rejection is rendered moot.

Further, the Examiner asserts that the word "derived" renders claim 9 indefinite. Applicant respectfully disagrees. As can be found, for example, on page 4, lines 26-27 of the instant specification, the term "derived" is clearly defined and therefore not indefinite. Further, one of ordinary skill in the art would know to what the term "derived", in the context of cells and tissues "derived" from a transgenic mouse, relates. In any case, the current claims do not use the term "derived." Newly added claim 24 uses the term "obtained, which term is clear and definite. Therefore, Examiner's rejection is rendered moot.

Applicant submits that amended claim 12 and new claims 21-30 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

***C. Rejection under 35 U.S.C. § 103***

Claims 1-8 and 10 stood rejected as being unpatentable under 35 U.S.C. § 103(a) based upon the teachings of Mansour *et al.*, 1988, *Nature* 336(24):348-352 ("Mansour"), in view of Weinberg *et al.*, 1996, *The Journal of Biological Chemistry* 271(28):16435-16438 ("Weinberg"). Applicant respectfully traverses this rejection.

Mansour describes a general approach for isolating embryonic stem cells containing a targeted mutation in a gene, provided that a cloned fragment of the gene is available.

Specifically, Mansour teaches the targeted disruption of the *hprt* gene and the proto-oncogene *int*-2 in mouse embryo-derived stem cells by homologous recombination using targeting constructs pRV9.1/TK and pINT-2-N/TK, respectively. The Examiner concedes, however, that Mansour does not teach how to make an NPY6 receptor targeting construct and knockout mouse.

Weinberg merely teaches the identification and cloning of a NPY6 gene.

As a basis of the obviousness rejection under 35 U.S.C. § 103, the Examiner asserts that the ordinary artisan would have been motivated to knock out the expression of the NPY6 gene in a mouse to study the role it plays in the complex biology of NPY and determine which NPY signaling pathway(s) it mediates, as suggested by Weinberg. The Examiner further asserts that the ordinary artisan would have had a reasonable expectation of success because of the teachings of Mansour and Weinberg. The Applicant respectfully disagrees.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must meet three basic criteria:

1. there must be some motivation or suggestion to modify the reference or combine reference teachings;
2. there must be a reasonable expectation of success; and
3. the prior art references must teach or suggest all the claim limitations.

There is no teaching in Weinberg that suggests the desirability of knocking out the NPY6 gene. On page 13 of the Office Action, the Examiner cites Weinberg as suggesting that NPY has various biological functions, including effects on anxiety, cardiovascular function and feeding behavior through interactions with distinct receptor subtypes. The Examiner further cites Weinberg as disclosing that the development of antisense oligonucleotides and NPY6 receptor-specific antibodies and ligands would help address the precise physiological role of this receptor.

The suggestions by Weinberg that the NPY6 receptor is involved in various biological functions and that the development of antisense oligonucleotides or NPY6-specific antibodies would help address the precise physiological role of the NPY6 receptor is not sufficient motivation to modify Weinberg or to combine Weinberg with Mansour to produce an NPY6 gene knockout mouse and, thus, to establish a *prima facie* case of obviousness. The mere fact that a reference can be modified does not render the invention obvious unless the prior art also suggests the desirability of the modification. In the instant case, Weinberg does not, in any way, suggest the desirability of knocking out the NPY6 gene, even as a way to further elucidate the

physiological role of the receptor.

The Examiner asserts that the ordinary artisan would have had a reasonable expectation of success because of the teachings of Mansour, who teaches a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Weinberg, who teaches the coding sequence of the mouse NPY6 gene. However, when combining references, the Examiner must show some teaching, motivation or suggestion to combine the references. The mere fact that the references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Further, the fact that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. Finally, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. In the instant case, there is no motivation to combine the teachings of Mansour with Weinberg to achieve the claimed invention. Mansour teaches a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a gene. There is no teaching or suggestion in Mansour as to the desirability of a targeted disruption of a NPY6 receptor gene. Similarly, Weinberg teaches the coding sequence of the NPY6 gene. However, there is no suggestion in Weinberg to create a targeted disruption of an NPY6 gene.

Finally, to establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. However, neither Mansour nor Weinberg, alone or in combination, teaches all of the limitations of the instant claims. For example, neither Mansour nor Weinberg teach or suggest a transgenic mouse with a disrupted NPY6 gene exhibiting a phenotype, particularly not a neuromuscular phenotype, or methods of making such a mouse, which inventions are the subject of the pending claims.

Applicant submits that amended claim 12 and new claims 21-30 are not obvious in view of the sole or combined teachings of Mansour or Weinberg and respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

Attached hereto as Appendix I is a marked up version of the amended claim indicating changes made.

It is believed that the claims are in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-639.

Respectfully submitted,

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Enclosures

## APPENDIX I

### Version With Marking To Show Changes Made

(Deletions are indicated by brackets; Insertions are indicated by underline)

In the claims:

12. (Amended) A method of identifying an agent [that modulates the function of a] capable of modulating a neuromuscular phenotype associated with NPY6 receptor, the method comprising:

(a) providing a [non-human transgenic animal] transgenic mouse comprising a homozygous disruption in a NPY6 receptor gene, wherein the transgenic mouse exhibits, relative to a wild-type mouse, a neuromuscular phenotype;

(b) administering [an] a putative agent to the [non-human transgenic animal] transgenic mouse; and

(c) determining whether the [function of the disrupted NPY6 receptor gene in the non-human transgenic animal] neuromuscular phenotype is modulated by the putative agent, thereby identifying an agent capable of modulating the neuromuscular phenotype.